POLICY CHALLENGES IN MALARIA VACCINE INTRODUCTION

MELINDA MOREE AND SARAH EWART

Malaria Vaccine Initiative, Program for Appropriate Technology in Health, Seattle, Washington

Abstract. Recently licensed life-saving vaccines have experienced slow introduction and gradual uptake in the developing world. Policy challenges at the national level contribute to the delay in making new vaccines accessible to people in poor countries. The hurdles that delayed the introduction of other vaccines can provide guidance for navigating the policy challenges that face the introduction of a new malaria vaccine. When a malaria vaccine is licensed, national leaders will rely on available data and analyses to draw conclusions about which malaria interventions have the greatest potential for public health impact. Epidemiologic and economic analyses can help facilitate their decision-making. This article draws attention to the importance of research to inform policy decisions and to minimize delays in the introduction of a new malaria vaccine.

INTRODUCTION

Malaria takes the lives of more than one million people per year, 90% of whom live in sub-Saharan Africa and causes 300–500 million people to fall ill. The majority of people who die of malaria are children less than five years of age. Malaria-related mortality has not decreased in the past decade, and by some estimates has actually increased. Maximum implementation of current anti-malarial interventions, such as insecticides, bed nets, and drugs, could decrease the malaria burden by half over the next 5–10 years.

Increasingly, international attention is focused on developing vaccines that can prevent malaria. New funding is allowing scientists from the public and private sectors to reinvigorate their efforts to accelerate malaria vaccine development. However, the slow uptake of life-saving vaccines in poor countries has shown that licensing a vaccine does not ensure its delivery to the developing world. There are multiple policy challenges in making a vaccine accessible to the people who need it most. This article highlights information that shapes national policy decisions about new vaccine introduction, and calls for further research to help inform decision-making processes around developing and implementing a malaria vaccine.

With many health needs and limited resources, national policymakers working in ministries of health and finance will want to know which interventions will have the greatest public health impact. When a new vaccine becomes available, decision-makers will have questions about it. Previous investigators have offered frameworks for such decision-making. Aylward and others proposed a framework for evaluating vaccines for use in the Expanded Program on Immunization (EPI).[1] Mansoor and others proposed a framework for assessing new vaccines.[2] Both frameworks, which can help in thinking about a future malaria vaccine, promote the consideration of multiple factors, such as burden of disease, expected impact of the vaccine, and implementation, financing, and supply issues. Figure 1 shows the likely factors in national decision-making about malaria vaccine introduction.

In the case of a new malaria vaccine, national policymakers will weigh the decision to introduce a malaria vaccine against competing demands for funding. Policymakers in malaria-endemic countries facing such a decision will want to compare the potential impact of a malaria vaccine, i.e., its ability to reduce morbidity and mortality rates, with the impact of other malaria control and treatment interventions. They will also want to compare it to the potential impact of other health and development interventions. The public health impact of a malaria vaccine will depend in part on the characteristics of the vaccine.

Without a licensed malaria vaccine, any discussion about a vaccine profile is purely hypothetical. The perfect malaria vaccine would be easy to deliver, have a lifelong duration of immunity, cost pennies, and demonstrate 100% efficacy against morbidity and mortality in people of all ages. Ideally, this malaria vaccine would be rapidly delivered to all countries, especially the poorest, to eradicate malaria.

The reality however, is that any malaria vaccine is unlikely to be perfect, and the decision to introduce the actual vaccine will pose policy challenges that will require further analysis. For example, a new malaria vaccine might cost dollars, rather than pennies, per dose. Also, future vaccines for complex diseases such as acquired immunodeficiency syndrome (AIDS), tuberculosis, and malaria might not be as efficacious as vaccines that are currently available for other diseases.

For the purposes of discussion, we propose a hypothetical malaria vaccine to illustrate the difficulties in predicting the public health impact of a vaccine. The hypothetical malaria vaccine will be delivered in three injectable doses, cost $10 per dose, and demonstrate 30–50% efficacy against severe disease for one year when administered to 1–4-year-old children. If this malaria vaccine were licensed, it would have the potential to save the lives of many children. Before introducing the vaccine, however, national policymakers would have to ask, "How many lives?" and "At what cost will they be saved?"

HISTORY OF VACCINE UPTAKE

Experience with other vaccines over the past two decades has shown that ensuring the accessibility of a vaccine is nearly as challenging as developing the vaccine itself. The slow introduction and uptake of hepatitis B (HB) and *Haemophilus influenzae* type b (Hib) vaccines reinforces the importance of information for decision-making.

The HB and Hib vaccines were licensed in the United States in 1981 and 1985, respectively, and both have experienced very slow uptake outside the industrialized world. Reasons offered for the slow uptake of these vaccines include not only their relatively high cost but also lack of disease burden and cost-effectiveness data to facilitate decision making.[3] When it was licensed, the HB vaccine was significantly more
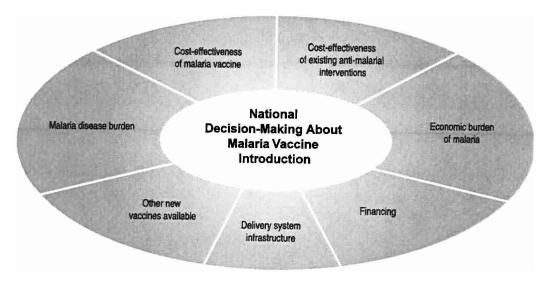
FIGURE 1. Factors informing national decision-making about malaria vaccine introduction.

expensive at $150 for the three required doses than other EPI vaccines, and leaders had insufficient information about the impact in their own countries. By 2001, 20 years after it first became available, nearly 75% of countries incorporated HB vaccine into their infant immunization programs and the price was down to nearly $1.50 for three doses.

Developing countries have also been slow to adopt Hib vaccine, which was recommended by the World Health Organization (WHO) for introduction into the EPI in 1997. By 2001, most countries using the Hib vaccine in routine immunization programs were high- and middle-income countries. Because of slow uptake in poor countries, the Vaccine Fund is now supporting the introduction of HB and Hib vaccines in the least-developed countries.

RESEARCH AND ANALYSIS INFLUENCE POLICY

After new vaccines are licensed, policymakers require information about the benefits of the vaccines over other interventions. They need information about the disease burden and the costs and impacts of currently available interventions to make decisions. Epidemiologic and economic data aid policymakers in decision-making about new vaccine introduction. Analysis of these data can facilitate the comparison of a range of options by illuminating their costs and benefits over time.[4,5]

In the absence of reliable national-level data, modeling is a useful tool to estimate health and economic data and predict outcomes. Miller and McCann used country-specific modeling to estimate the impact of vaccination at the national level with HB, Hib, *Streptococcus pneumoniae*, and rotavirus vaccines.[4] They concluded that these four vaccines are highly cost-effective (e.g., the costs of saving a life-year are less than the per capita gross national product), especially in low-income countries.[4] Their research supports the argument that these new vaccines, if introduced, have the potential to prevent hundreds of thousands of deaths worldwide. Modeling the impact of malaria vaccines could prove that they are also cost-effective.

When a malaria vaccine is available, such quantitative analysis will help inform the decisions of national policymakers. Their questions might include What is the malaria disease burden (morbidity, disability, and mortality rates) in this country? What is the economic burden of malaria in this country? What other health interventions to fight malaria currently exist in this country? Of these interventions, which will have the greatest public health impact? Which interventions are the most cost-effective? Which combination of interventions should this country adopt? If a malaria vaccine proves cost-effective, can this country afford it? If not, who will pay for the vaccine? What financing options are available? Can this country's current health infrastructure accommodate delivery of the vaccine? Does this country have sufficient human resources to administer this vaccine? What other factors (e.g., burden of other diseases, international influences, and political pressures) should be taken into consideration? Depending on their national circumstances, each country could answer the questions differently, placing relative importance on different factors.

MALARIA DISEASE BURDEN

While malaria is recognized as a public health problem in endemic countries, national statistics about the malaria disease burden are generally unavailable or unreliable. National surveillance systems are often weak or nonexistent. Since patients who are unable to afford treatment in health centers frequently treat themselves, clinical data paint an incomplete picture. Even malaria cases treated in clinics might be documented inaccurately since diagnostic tools are rare and febrile illnesses might be misdiagnosed.

Using international estimates, most experts concur that malaria takes the lives of more than one million people every year, and some estimates suggest that as many as 2.7 million people die of malaria each year. Approximately 90% of the malaria deaths that occur each year take place in Africa and can be attributed to *Plasmodium falciparum*.[6] The WHO estimates malaria's global burden in terms of disability-adjusted life years (DALYs), representing the present value of a future without malaria disability or death. The WHO currently attributes 42,280,000 DALYs to malaria worldwide.[7]

Data sources for malaria are gradually improving. Over the past 10–15 years, considerable efforts have been made to improve health information and malaria surveillance. Since 1995, the African Malaria Vaccine Testing Network (AMVTN), now renamed the African Malaria Network Trust (AMANET), has encouraged and promoted the collection of epidemiologic data on malaria, especially to support malaria vaccine trials in Africa. Demographic surveillance systems (DSS) provide long-term information about the health of large populations, track new health threats, and evaluate health interventions, including malaria vaccine research. Since 1998, the INDEPTH Network, an international network of DSS sites, has been facilitating cross-site studies and impact assessments. Current malaria vaccine trials are being conducted near these DSS sites.

Some demographic and health surveys (DHS) conducted since 1998 have included malaria-relevant indicators that facilitate cross-country comparisons. National health management information systems (HMIS) are strengthening their own malaria surveillance. Integrated disease surveillance (IDS) has also begun to provide early detection and prediction of malaria epidemics in Africa. The Mapping Malaria Risk in Africa (MARA) collaboration was established to map malaria in Africa using geographic information system capacity. Even with these improved information systems, more consistent and reliable information about the epidemiology of malaria is needed. Additional DSS sites and consistent use of malaria modules in DHS studies can improve policymakers' understanding of the malaria disease burden in their countries and enable them to make better decisions.

CHOICES OF MALARIA INTERVENTIONS

When national policymakers evaluate malaria interventions, they will want to determine which intervention or combination of interventions (such as insecticides, drugs, and mosquito nets) to implement. When a vaccine becomes available, they will also want to determine its impact. For example, using the hypothetical malaria vaccine, what does it mean at the national level when a vaccine has 30–50% efficacy against severe disease in 1–4-year-old children? How does this affect morbidity and mortality rates in each country? Even a vaccine that has low-to-moderate efficacy can save the lives of hundreds of thousands of children. However, to what extent will policymakers be receptive to low-to-moderate efficacy levels in malaria vaccines, given the high level of efficacy found in the majority of current EPI vaccines?

Researchers working on vaccines against human immunodeficiency virus (HIV) have examined the demand for low-to-moderate and high-efficacy vaccines. The WHO, the Joint United Nations Program on HIV/AIDS (UNAIDS), and the International AIDS Vaccine Initiative (IAVI) held regional workshops in 2001 to discuss the policy challenges related to introducing a preventive HIV vaccine. Regional health and political leaders and community representatives reported that even HIV vaccines with low-to-moderate efficacy (e.g., those that are 30–50% efficacious) against infection and disease would be favored as prevention tools, especially for high-risk populations. High-efficacy vaccines (e.g., 80–90% efficacious)

would be in greater demand and could be used more broadly across the population.[8]

The extent to which this information can be generalized for malaria is not clear. Policymakers in endemic countries may or may not be similarly receptive to low-to-moderate efficacy malaria vaccines, especially for children. Before making a decision about a new vaccine, leaders must carefully study epidemiologic data to determine which malaria intervention or combination of interventions has the greatest potential for reducing the disease burden. Comparison of multiple malaria control measures will also include economic analysis.

ECONOMIC ANALYSIS OF MALARIA INTERVENTIONS

Another key consideration for policymakers will be determining which malaria intervention provides the greatest impact for the lowest cost. Cost-effectiveness analysis, measured in terms of the cost required to achieve a particular health outcome, can inform economic decision making about vaccine policy.[4,5,9] While EPI vaccines are considered to be highly cost-effective, with low costs per dose, a malaria vaccine might be more expensive. Studies using hypothetical malaria vaccines with varying costs and efficacies can be used to assign target values at which a vaccine will be cost-effective.[9]

Researchers have begun speculating about what might constitute a minimally acceptable vaccine for the developing world. Proposed efficacy levels for cost-effective malaria vaccines range from low to high. Genton and Corradin suggest that a malaria vaccine with greater than 50% efficacy might be highly cost-effective for endemic areas.[10] Engers and Godal estimate that a hypothetical malaria vaccine that could be introduced into the EPI with 30% or higher efficacy against child mortality and a duration of immunity of three years or more would be highly cost-effective.[11] Once a vaccine is available, policymakers will need to consider efficacy, costs, dosing schedules, and the cost of other interventions before they decide whether to introduce the vaccine.

FINANCING VACCINES

Policymakers will also need to explore financing mechanisms before the vaccine is licensed. Current malaria control measures are funded by a combination of governments, donors, and private individuals. National leaders may ask whether the national government be willing to pay for a malaria vaccine. Exploring financing for current malaria interventions can provide an indication of willingness to pay for a malaria vaccine.

African governments generally support malaria control and treatment efforts by paying for health systems and administration budgets, while donors and private individuals fund the remaining costs. The United Nations Children's Fund (UNICEF) estimates that African governments each spend an average of $300,000 annually to implement malaria control programs. For a country of five million people, this amounts to about $0.06 per person.[12] African governments' total per capita health spending ranges from $1 to $120.[13] Given costs and dosing schedules, policymakers will need to determine whether national health spending on malaria can stretch to accommodate the cost.

If national governments cannot afford a malaria vaccine, policymakers may have to search for other funding mechanisms. It will be important to consider international donors' and households' support for malaria control because these levels of support might be indicative of willingness to pay for a malaria vaccine. Contributions by households and donors presently make up the bulk of health care and malaria control expenditures in Africa. In 2002, donors earmarked an estimated $200 million to support malaria control and prevention efforts worldwide.[12] Policymakers will need to determine whether donors will commit to paying for a malaria vaccine for low-income countries, as they have committed to pay for HB and Hib vaccines. International organizations such as the Global Alliance for Vaccines and Immunization (GAVI) and its financial partner, The Vaccine Fund, may be additional resources.

Throughout these deliberations, countries must focus on financing strategies that result in the long-term sustainability of the programs. At the household level, monthly expenditures on malaria-related control and treatment can be very high, especially for low-income families. While data on household expenditures on malaria vary by country and focus largely on urban households, estimates range from $0.23 to $15 per household for prevention and $1.79–$25 per household for treatment.[14] Will individuals be willing or able to pay for a malaria vaccine? If so, how much can they afford to pay? Will they be able to afford other malaria control interventions at the same time? At $10 per dose, most households in low-income countries will find this cost prohibitive for one child, let alone several children.

DELIVERY SYSTEM INFRASTRUCTURE

Policymakers must also consider how to deliver a malaria vaccine to the country's citizens. Health infrastructures are already established to deliver EPI vaccines in routine immunization schedules. New vaccines must be carefully evaluated before being introduced into the EPI system. Criteria include appropriateness as a control strategy for the disease, efficacy and safety of the vaccine, compatibility with other antigens, adequate and affordable supply, and ability to be delivered.[1]

The ideal malaria vaccine would be a vaccine for infants that can be introduced into the EPI. However, when a malaria vaccine first becomes available, technologic barriers may make it incompatible with the EPI. If faced with such a barrier, policymakers at the national level will have to evaluate their health infrastructures to assess whether they can accommodate a malaria vaccine outside the current EPI system.

OTHER CONSTRAINTS TO NEW VACCINE INTRODUCTION

In addition to the national-level policy challenges mentioned, regulatory and manufacturing challenges can affect the introduction of new vaccines. Regulatory challenges can slow the introduction of a malaria vaccine. Without international coordination of vaccine regulatory structures, each country may introduce delays in decision-making about vaccine safety and appropriateness. Manufacturing challenges can also impede rapid uptake of a new malaria vaccine. Pharmaceutical companies must manufacture a supply that is suf-

ficient to meet demand. Years before licensure, companies must project vaccine demand so that they can build appropriate manufacturing capacity. If demand for a malaria vaccine exceeds manufacturing supply, countries could wait years before gaining access to sufficient supplies.

IMPORTANCE OF CURRENT RESEARCH

This article describes the issues that must be researched before the introduction of a malaria vaccine. Clearly, better epidemiologic data is needed on all populations affected by malaria, especially in sub-Saharan Africa. Disease burden studies and stronger country-level malaria surveillance systems help policymakers understand the extent of the malaria problem in their nation. Existing efforts, such as DSS, DHS, and HMIS, should be strengthened and expanded to more countries. Cost-effectiveness studies on malaria control and hypothetical malaria vaccines are also essential to building a strong foundation for the introduction of a malaria vaccine. Country-specific studies on the economic burden of malaria are needed to facilitate prioritization of national health budgets. Marketing and demand studies are needed to determine who can pay for a malaria vaccine and to whom it can be delivered. To the extent possible, these studies should be specific to particular countries or regions with similar transmission settings, since questions will be answered at the national level. Even with incomplete information, modeling studies can begin to project answers to some of these important questions now.

CONCLUSION

With access to relevant epidemiologic and economic data before licensure of a malaria vaccine, policymakers can make timely decisions about its introduction. Given the enormous morbidity and mortality associated with malaria, any delay in making a preventive vaccine accessible to sub-Saharan Africa is intolerable. Preparing the answers to these key policy questions in advance will minimize delays in introducing a malaria vaccine and thus save millions of lives.

Authors' addresses: Melinda Moree and Sarah Ewart, Malaria Vaccine Initiative, Program for Appropriate Technology in Health, 1455 NW Leary Way, Seattle, WA 98107, Telephone: 206-285-3500, Fax: 206-285-6619, E-mail: mmoree@path.org.

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